Intraperitoneal Application of Bupivacaine During Laparoscopic Cholecystectomy—Risk or Benefit?

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We investigated, in a double-blind study, the effects of intraperitoneal local anesthetics during laparoscopic cholecystectomy. In Part A of the study 30 patients received 50 mL saline 0.9% (A 0), bupivacaine 0.125% (A 125), or bupivacaine 0.25% (A 25) intraperitoneally at the end of surgery. Mean maximum plasma concentrations of bupivacaine reached 0.48 mg/L (range 0.15–0.90 mg/L) in Group A 125 and 1.0 mg/L (0.35–2.10 mg/L) in Group A 25 within 15 min (range, 5–30 min). There was no significant difference in pain scores or opioid consumption (patient-controlled analgesia with piritramid): 24, 28, and 13 mg/24 h among the study groups, respectively (not significant). Postoperative respiratory function deteriorated in comparison to preoperative values in all study groups, but the forced vital capacity was significantly more impaired in Group A .25. In Part B, 24 patients received placebo (B 0) or bupivacaine 0.25% (B 25). Postoperative hypoxemic periods (oxygen saturation < 92%) were significantly more frequent in Group B 25. Considering the questionable benefits and the potential risks, we would not recommend the application of intraperitoneal bupivacaine during laparoscopic cholecystectomy.

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Laparoscopic cholecystectomy has become a standard technique for gall bladder surgery. Benefits in comparison to conventional laparotomy are shorter lived effects on pulmonary function and less postoperative pain (1,2). However, patients often suffer from considerable pain during the first 24 postoperative hours (3–5). Therefore, the following study addresses the question of whether the intraperitoneal application of local anesthetics yields any benefit in regard to postoperative pain and pulmonary function after laparoscopic cholecystectomy.

Methods

The study was approved by our ethics committee and all patients gave their written, informed consent. Fifty-four patients scheduled for laparoscopic cholecystectomy were included in this prospective, randomized, placebo-controlled, and double-blinded study. All procedures were performed by the same anesthesiology and surgical teams.

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Anesthesia was induced with 2.5 mg dihydrobenzperidol, 0.05 mg fentanyl, 0.25 mg/kg etomidate, and succinylcholine 1.5 mg/kg to facilitate the intubation of the trachea. Anesthesia was maintained with isoflurane (0.5–1.5 vol%), O_2/N_2O (30%/70%), and atracurium. Further intraoperative opioids were restricted to a single bolus dose of 0.1 mg fentanyl.

The aim of Part A was to evaluate the appropriate concentration of bupivacaine. Thirty patients were allocated to one of the following groups: Group A 0, 50 mL saline 0.9%; Group A 125, 50 mL bupivacaine 0.125%; or Group A 25, 50 mL bupivacaine 0.25%. Blinded solutions were prepared by our pharmacy department and were given intraperitoneally at the end of the operation through the operation trocars. Twenty-five milliliters was applied directly to the gall bladder bed on the liver and the other 25 mL subphrenically.

Venous blood samples (3 mL) were drawn from the forearm opposite to the intravenous infusion to determine plasma concentrations of bupivacaine and were measured as described previously (6,7). Pharmacokinetic data were calculated using GraphPad InPlot (GraphPad, San Diego, CA).

Plasma concentrations of α_1-acid glycoprotein, a major binding site for local anesthetics in plasma, were determined in duplicate by radial immune diffusion (Behring, Marburg, Germany). The protein binding of bupivacaine was assayed by equilibrium

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dialysis (6) in those samples with the highest individual total bupivacaine content. Free (unbound) concentrations were calculated.

Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and peak flow were recorded (Respiradyne; Chesebrough-Pond's Inc., Greenwich, CT) the evening before operation and for the next 4 days thereafter (always at 6PM).

Postoperative analgesia was started with a bolus dose of 7.5 mg piritramid. Afterward, the patients intravenous (IV) line was connected to a patient-controlled analgesia (PCA) device set with the following variables: bolus dose piritramid 5 mg and lockout time 10 min, without background infusion. The consumption of piritramid was evaluated for the first 24 h.

All patients estimated their pain using a numeric rating score (0–10). Four hours after operation they assessed the location of pain and the pain scores at rest, during deep inspiration, and coughing. This procedure was repeated on the first, second, and third postoperative days in analogy to the spirometry.

Since Part A of the study revealed a trend toward a smaller analgetic consumption, but a more profound reduction in FVC, we wanted to evaluate pain scores, opioid demand, vigilance, and effects on oxygenation in the early postoperative period more closely. Therefore, in Part B of the study, saline 0.9% (Group B 0, $n = 12$) was compared with bupivacaine 0.25% (Group B 25, $n = 12$) only. Initially piritramid was titrated in steps of 3.75 mg. Smaller bolus doses of piritramid (2 mg) for PCA were used to obtain better differentiation. Pain scores were rated by the patient each hour for the first 6 h using a visual analog scale (0–10). In addition, vigilance, nausea, vomiting, and tolerance of pain were assessed on a scale from 1 (no symptoms) to 5 (adverse result). Oxygen saturation was measured online by pulse oximetry during the first 4 h.

Median differences were checked for by Kruskal-Wallis test or Wilcoxon test and frequencies by χ^2 test. α was set at 0.05; β at 0.10. For calculations of correlation SIMSTAT® (Provalis Research, Canada) was used.

Results

There were no significant differences between the groups regarding biometric data, former experience with postoperative pain, chronic analgetic consumption, or operation variables. No significant differences in vigilance (Table 2), nausea, or vomiting were seen. The only perioperative complications were an umbilical abscess (A 0) and two cases of thrombophlebitis at the IV, site (A 125; B 25). The postoperative duration of hospital stay did not differ (4.4–4.7 ± 0.6 days in all groups).

Only 13% of the patients did not take the opportunity to get pain relief by using the PCA device. There were no significant differences in consumption of analgesics or pain scores (at rest, inspiration, coughing) between the groups studied, just a trend toward a smaller piritramid consumption during the first 24 h in the group receiving bupivacaine 0.25% in Part A of the study (medians: A 0; 25 mg [0–35 mg]; A 125, 27 mg [10–45 mg]; A 25, 5 mg [0–65 mg]). However, using a more sophisticated PCA dose regimen in Part B of the study, no differences between the groups could be found (medians: B 0, 18 mg [2–44 mg]; B 25, 13 mg [0–46 mg]). In particular, a close examination of the use of piritramid during the first 6 h after operation (a period for which a regional analgesic effect of bupivacaine would be expected) revealed no significant differences. The β error for not discovering a difference of more than 7.5 mg piritramid/24 h was calculated to be less than 0.10. The self-estimated pain scores did not show any significant differences between the study groups (Tables 1 and 2). The incidence of pain at particular sites was not influenced by the administration of intraperitoneal local anesthetics. Shoulder pain was reported by eight patients (A 25, 2; A 125, 4; A 0, 3; B 0, 1; B 25, 0).

Respiratory function deteriorated significantly after laparoscopy in all groups. Vital capacity was significantly more reduced in Group A 25. For example, median FVC values 4 h after operation in comparison to values before the operation were: A 0, 59%; A 125, 35%; and A 25%, 33% (Fig. 1). Other respiratory variables (peak flow, FEV) followed the same deteriorating trend without reaching statistical significance. In accordance with these respiratory variables, hypoxemic periods ($Sao_2 < 92\%$) were documented more often ($P < 0.05$) in Group B 25 than in Group B 0 (Fig. 2).

The mean maximum plasma concentration of bupivacaine after bupivacaine 0.125% was 0.48 mg/L (range, 0.15–0.9 mg/L) occurring 5–20 min after injection (mean, 18 min). With application of bupivacaine 0.25%, maxima ranging from 0.35 to 2.1 mg/L (mean, 1.0 mg/L) were found after 5–30 min (mean, 15 min) (Fig. 3). In one patient (A 25) the maximum plasma concentration exceeded the threshold value of 2 mg/L for approximately 20 min. However, no clinical signs of neuro- or cardiovascular toxicity were observed. Terminal elimination half-life ($t_{1/2}$ β), as calculated from Figure 3 using an exponential decay starting at 30 min, was 102 min.

α-Acid glycoprotein did not differ between the study groups: 0.73 ± 0.13 mg/dL (range, 0.54–1.0) A 0, 0.71 ± 0.15 mg/dL (range, 0.43–1.03) A 125, and 0.80 ± 0.2 mg/dL (range, 0.57–1.32) A 25 (normal values, 0.9 [0.55–1.4]). The protein binding of bupivacaine was 88% ± 2% (range, 84%–92%) A 125, and 90% ± 2%

Table 1. Pain Scores After the Intraperitoneal Administration of Bupivacaine During Laparoscopic Cholecystectomy in Part A of the Study.

	Day of operation			Postoperative Day 1			Postoperative Day 2			Postoperative Day 3		
Pain	A 0	A 125	A 25	A 0	A 125	A 25	A 0	A 125	A 25	A 0	A 125	A 25
At rest												
Median	3.0	1.5	3.0	1.0	2.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0
Confidence interval (5–95)	0.0–4.5	0.0–6.5	0.0–5.0	0.0–4.0	0.0–3.5	0.0–2.0	0.0–4.0	0.0–6.0	0.0–1.0	0.0–3.0	0.0–1.0	0.0–3.0
During inspiration												
Median	3.5	5.0	4.0	4.0	2.0	2.0	0.0	3.5	1.0	0.0	1.0	1.0
Confidence interval (5–95)	1.0–8.0	1.0–7.0	0.0–9.0	0.0–6.5	1.0–4.5	0.0–4.0	0.0–5.0	0.0–7.0	0.0–2.0	0.0–4.0	0.0–4.0	0.0–3.0
At coughing												
Median	3.0	5.5	5.0	5.0	4.0	5.0	3.0	3.5	4.0	2.0	0.0	3.0
Confidence interval (5–95)	0.0–6.0	0.0–7.0	2.0–10.0	0.0–6.0	2.0–8.0	1.5–8.0	0.0–6.0	1.0–8.0	0.0–8.5	0.0–5.0	0.0–5.0	0.0–8.5

Ranking scales (0–10) for pain at rest, pain during inspiration, and pain at coughing.
A 0 = saline 0.9%; A 125 = bupivacaine 0.125%; A 25 = bupivacaine 0.25%.

Table 2. Vigilance and Pain Scores After the Intraperitoneal Administration of Saline 0.9% (B 0) or Bupivacaine 0.25% (B 25) During Laparoscopic Cholecystectomy in Part B of the Study.

	Hours after operation													
	1		2		3		4		5		6		24	
	B 0	B 25	B 0	B 25	B 0	B 25	B 0	B 25	B 0	B 25	B 0	B 25	B 0	B 25
Pain score														
Median	0.5	1.0	2.0	1.0	1.5	1.0	1.0	1.0	1.0	1.5	1.5	1.5	0.0	1.0
Confidence interval (5–95)	0.0–1.0	0.0–4.0	0.0–3.0	0.0–3.0	0.0–4.0	0.0–3.0	0.0–4.0	0.0–3.0	0.0–3.0	0.0–2.0	0.0–4.0	0.0–3.0	0.0–1.0	0.0–2.0
Vigilance														
Mean	2.6	2.8	2.4	2.8	2.0	2.5	2.1	2.3	2.0	2.1	1.9	1.9	1.3	1.0
SD	0.7	0.7	0.8	0.8	0.7	0.9	0.8	0.9	1.0	0.9	0.9	1.0	0.7	0.0
Minimum	1.0	2.0	1.0	2.0	1.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Maximum	3.0	4.0	3.0	4.0	3.0	5.0	3.0	4.0	3.0	4.0	3.0	4.0	3.0	1.0

Pain score = visual analog scale, 0–10; vigilance = 1, awake; 2, easy to awake; 3, tired; 4, strongly sedated; 5, not arousable.

(range, 85%–92%) in A 25 (not significant). Maximum free (unbound) concentrations were calculated: 0.05 ± 0.02 mg/L (range, 0.02–0.09 mg/L) A 125, and 0.11 ± 0.06 mg/L (range, 0.04–0.29 mg/L) in A 25 ($P < 0.05$). No significant correlation between protein binding and plasma concentration of this protein could be shown ($r = 0.35$; $P = 0.07$).

Discussion

Several approaches have been attempted to minimize postoperative pain after laparoscopy. Previous investigations addressed the question of whether local anesthetic infiltration of the trocar insertion sites is profitable. According to a review by Dahl et al. (3), only 3 of 13 placebo-controlled studies showed a significant, clinically relevant advantage of wound infiltration.

After gynecologic laparoscopy (8,9) and laparoscopic cholecystectomy (4) no significant clinical benefits of wound infiltration could be demonstrated. Reports on the effects of intraperitoneal local anesthetics on postoperative pain have been scanty up to now. Helvacioglu and Weis (9) compared three groups of patients after gynecologic laparoscopy: 1) intraperitoneal lidocaine plus incisional bupivacaine; 2) incisional bupivacaine; 3) control. Group I had significantly lower pain scores and opioid demand in the recovery unit, whereas at 24 h postoperatively there was no significant difference. This study was not double-blinded and a regimen of meperidine IV and intramuscularly as needed was used rather than PCA. Narchi et al. (10,11) evaluated four groups after gynecologic laparoscopy without a double-blind study-design: 1) control; 2) saline; 3) 80 mL of lidocaine 0.5% with adrenaline; and 4) 80 mL bupivacaine 0.125% with adrenaline subdiaphragmatically. The patients of Groups 3 and 4 had a lower incidence of shoulder pain (not significant at all time points of measurement). There was no difference in pain at other locations. The use of postoperative analgesics in this study was not reported. In a recent study, Rademaker et al. (12)

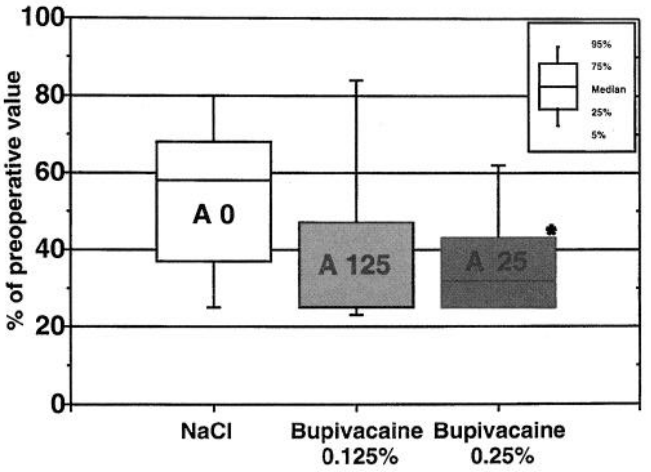

Figure 1. Forced vital capacity 4 h after laparoscopic cholecystectomy with intraperitoneal administration of saline 0.9% (A 0), bupivacaine 0.125% (A 125), and 0.25% (A 25) during laparoscopic cholecystectomy. Values in percent of preoperative data. $*P < 0.05$, A 0 vs A 0.25%. A 0 = saline 0.9%; A 125% = bupivacaine 0.125%; A 25 = bupivacaine 0.25% in Part A of the study.

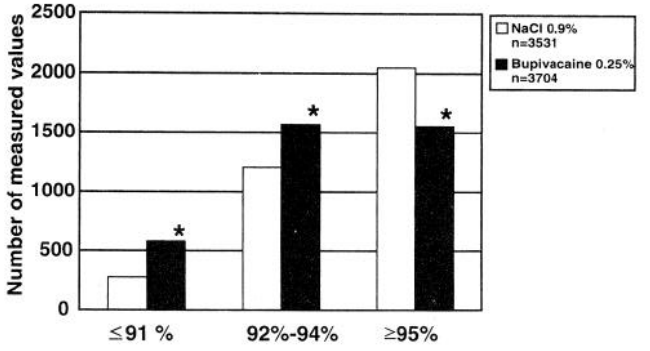

Figure 2. Oxygen saturation during the first 6 h after laparoscopic cholecystectomy (50 mL NaCl 0.9% versus bupivacaine 0.25% intraperitoneally). Number of measurements with oxygen saturation ≤ 91%, 92%–94%, and ≥ 95%. $*P < 0.05$, B 0 vs B 25. B 0 = saline 0.9%; B 25% = bupivacaine 0.25% in Part B of the study.

found no decrease in postoperative pain scores or opioid consumption (nicomorphine intramuscularly on request) after 20 mL lignocaine 0.5% or 20 mL bupivacaine 0.25%. Another recent study using lower volumes (20 mL 0.25%) of bupivacaine showed no reduction of pain or supplemental metamizol and tramadol (13).

This is the first investigation of the effect of an intraperitoneal local anesthetic in patients after laparoscopic cholecystectomy using a PCA evaluation of opioid demand. No significant benefit in regard to postoperative pain scores or opioid demand could be demonstrated. That our results contradict those of some of the above-mentioned studies is most possibly due to a difference in study populations (gynecologic laparoscopy versus laparoscopic cholecystectomy), or to our more sophisticated evaluation of postoperative pain using PCA. Judging from our pharmacokinetic

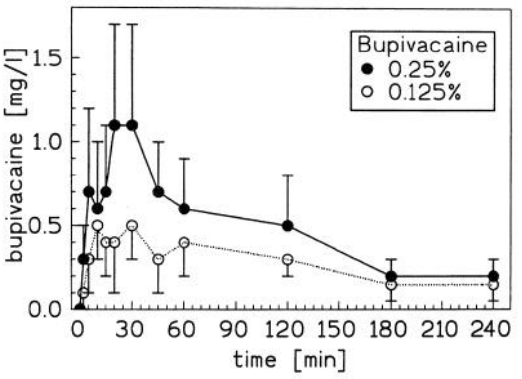

Figure 3. Plasma concentrations of bupivacaine after intraperitoneal administration of bupivacaine 0.125% (open circles) and 0.25% (closed circles) during laparoscopic cholecystectomy.

data, it is not advisable to evaluate higher doses of bupivacaine intraperitoneally.

Differences in analgesic consumption between Parts A and B were probably caused by a rather high loading dose (7.5 mg) and bolus dose (5 mg) of piritramid in Part A. Furthermore, in Part A, 33% of the patients did not take the opportunity of using the PCA. Realizing that analysis of pain scores in Part A during the first 3 h was difficult (due to sedation), we reduced the loading and bolus doses in Part B. Regarding total analgesic consumption, it became evident that with higher loading doses fewer patients used further PCA. Opioid consumption with PCA seems to be a function of the bolus. In both parts (A 0; B 0) the number of demanded boluses did not differ, confirming results reported by Lehmann (14).

Maximum plasma concentrations of bupivacaine after intraperitoneal application of 50 or 100 mg occurred after 5–30 min with a mean of 0.48 and 1.0 mg/L, which resembles other techniques of regional anesthesia such as brachial plexus or epidural blockade (15). No side effects attributable to the local anesthetics were noted and there was no significant difference in postoperative vigilance between the study groups. Rademaker et al (10) observed peak plasma concentrations of bupivacaine 0.5 ± 0.3 mg/L 15 min after application of 20 mL bupivacaine 0.25%. During gynecologic laparoscopy Spielman et al. (16) reported maximum plasma concentrations of 0.2–0.77 mg/L with a peak 60 min after 20 mL bupivacaine 0.5%. Narchi et al. (11) used 80 mL of bupivacaine 0.125% with epinephrine 1/800,000 resulting in a mean maximum plasma concentration of 0.92 mg/L at 52 min. In comparison to our study results, these maxima are somewhat lower and occurred rather late. Several reasons could account for these differences: the lower dose applied (12), the different location of intraperitoneal application [Fallopian tube (16)], the use of vasoconstrictors (11) and the time of application [before the

start of pelvic exploration (11,16)], since the high intraabdominal pressure during capnoperitoneum may slow absorption from the peritoneal surface.

The concentration of the binding protein, α_1-acid glycoprotein was within the normal range during the operation, resulting in a protein binding of approximately 90% or free fraction of 0.1, respectively. Therefore, the calculated free concentrations were rather high. In one patient in Group A 25% the maximum free concentration of bupivacaine was above the presumed threshold level for central nervous system toxicity of 0.24 mg/L (17).

Since α_1-acid glycoprotein is an acute phase protein, its concentration is increased in the postoperative period. Accordingly, a previous investigation showed a reduced free fraction of bupivacaine postoperatively of approximately 0.03 (6).

In the present study a significant impairment of pulmonary function after laparoscopic cholecystectomy became evident in all groups. Up to the third day FVC, FEV_1 and peak flow had not recovered completely to preoperative values [in accordance with data reported by others (1,18,19)]. Nevertheless, postoperative recovery of respiratory function after laparoscopic surgery is obviously faster compared to open cholecystectomy (2,20,21).

Improvement in postoperative pain relief could contribute to a better respiratory performance. Nevertheless, abdominal pain is probably not the predominant reason for impaired postoperative pulmonary function. Diaphragmatic dysfunction in the early postoperative period results from open upper abdominal surgery (22) and from laparoscopic cholecystectomy alone, in contrast to findings after laparoscopic hernia repair (23). Hemidiaphragmatic paresis is a well known side effect of regional anesthesia techniques such as interpleural (24) and brachial plexus block (25). In the groups receiving bupivacaine intraperitoneally the decrease in FVC and the tendency to hypoxemic episodes was even more pronounced, at least in the first hours after the operation (the approximate duration of a bupivacaine-induced blockade). Therefore, a (partial) paresis of the phrenic nerve due to the local anesthetic blockade could have amplified this effect.

We conclude that the administration of bupivacaine up to a dose of 125 mg intraperitoneally after laparoscopic cholecystectomy fails to provide significant analgesic benefit. Since significant side effects on pulmonary function and oxygen saturation occur, we do not recommend intraperitoneal local anesthetics for pain therapy after laparoscopy.

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